

The MyVal Transcatheter Heart Valve System for the Treatment of Severe Aortic Stenosis – Current Evidence and Future Directions

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Transcatheter aortic valve replacement has revolutionised the treatment of aortic valve disease. The MyVal™ device (Meril Life Sciences Pvt. Ltd., Gujarat, India) is a CE-marked, next-generation balloon-expandable transcatheter heart valve, designed for the treatment of severe aortic valve stenosis. This review illustrates the salient technical feature of this transcatheter valve, pre-clinical studies, and evidence from the first in-human trial. We also provide a brief overview of planned clinical trials and registries.

Keywords

Transcatheter aortic valve implantation, balloon-expandable, transcatheter heart valve, newer-generation transcatheter heart valve, severe aortic stenosis

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Aortic stenosis is a common degenerative valve disease and its prevalence increases with age.¹ If untreated, severe symptomatic aortic stenosis leads to significant morbidity and mortality.² Although surgical aortic valve replacement (SAVR) is a well-established treatment option for this condition, more than 30% of patients are not suitable candidates for SAVR due to increased operative risks; advanced age and age-related frailty; left ventricular dysfunction; and multiple comorbidities, including pulmonary and renal dysfunction.^{3,4} Transcatheter aortic valve replacement (TAVR), a percutaneous, minimally-invasive, cathlab-based procedure, was first performed by Alan Cribier et al. in 2002, and has revolutionised the treatment of calcific aortic stenosis in the elderly.⁵ With increasing favourable evidence from registries and randomised trials versus SAVR, TAVR has now become the new standard of care for elderly patients with calcific aortic stenosis.^{6–9}

Although TAVI started as an alternative treatment for patients with severe aortic stenosis who were deemed inoperable or at high-risk for SAVR,^{10,11} it has now shown advantages and superiority to SAVR even in low surgical-risk patients. With rapidly increasing numbers of patients and widening indications, there is an unmet need to further improve the technology in order to reduce the procedural risks of conduction disturbance, paravalvular leak, stroke and vascular complications, making the procedure safer for the patient and less complex for the operator.

The MyVal™ transcatheter heart valve (THV) (Meril Life Sciences Pvt. Ltd., Gujarat, India) is a CE-marked, newer-generation balloon-expandable TAVR system. After initial animal studies and early data from the first in-human MyVal-1 study, which demonstrated safety and effectiveness of the MyVal THV for the treatment of severe aortic stenosis in patients at intermediate or high-risk for surgery,¹² the MyVal THV was approved by the Drug Controller General of India (DCGI) in October 2018. To date, more than 1,300 patients worldwide have been treated with the MyVal THV. This review summarises the salient technical features of the MyVal THV device, clinical experience and the published and ongoing trials and registries.

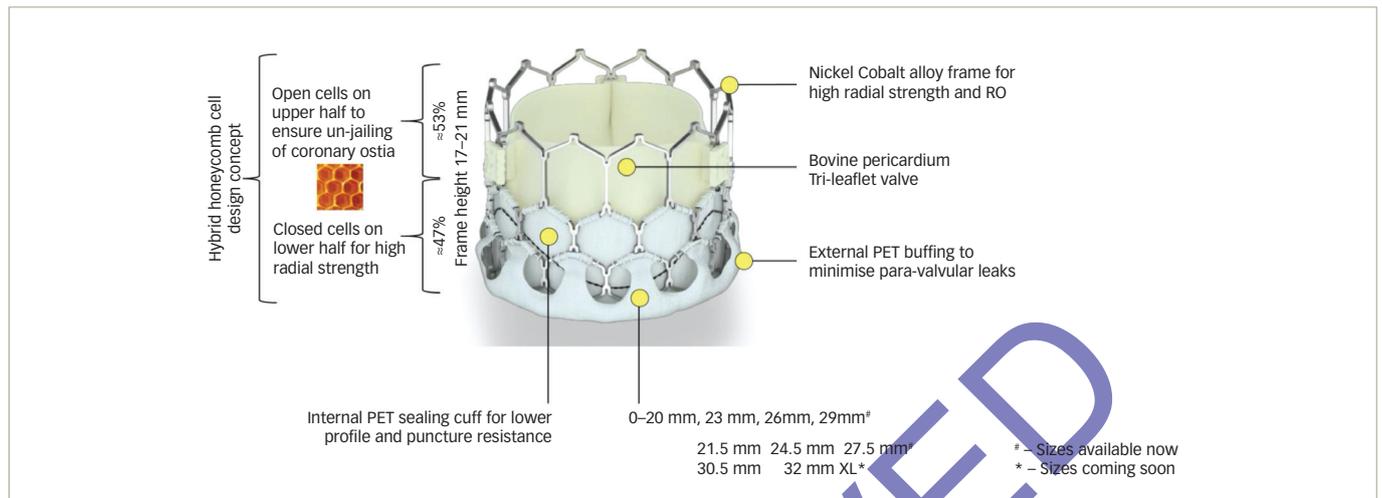
Technical features of the Myval transcatheter heart valve system

The MyVal THV system is made up of three main components: the valve, delivery catheter and the introducer sheath.

The valve

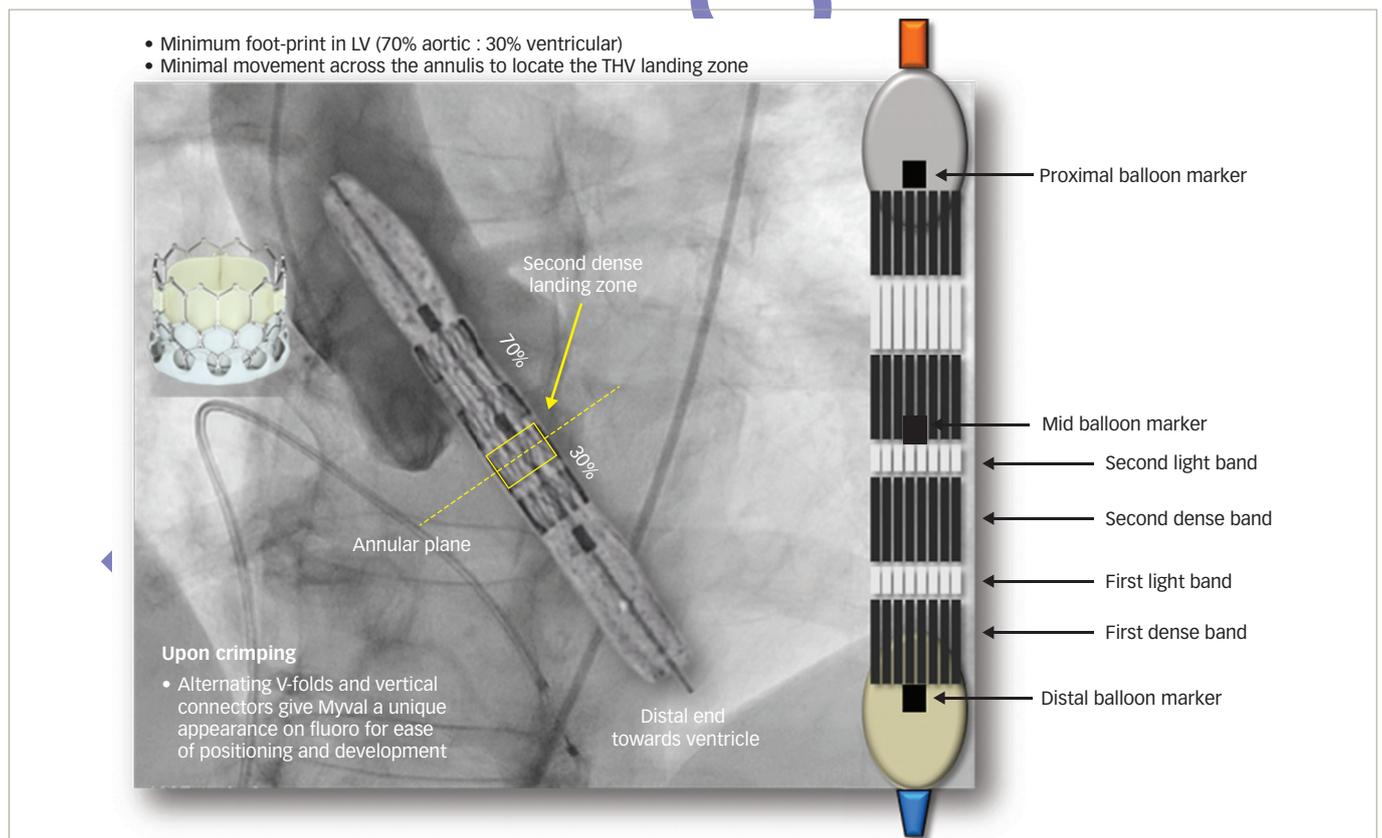
The valve consists of a tri-leaflet, decellularized, bovine pericardial valve treated with anti-calcification treatment and fixed at three equipoise vertical commissural posts (separated by 120 degrees) on the metal frame. The nickel–cobalt alloy stent frame is composed of a single design element – hexagons, arranged in such a fashion that allows large open cells to occupy 53% of the frame towards the aortic end and closed cells to occupy 47% of the frame towards the ventricular end (*Figure 1*). The open cells in the upper half prevent the jailing of the coronary ostia, whereas the closed cells in the lower half provide high radial strength. The valve frame, after crimping, gives a unique dark–light alternating band pattern (attributed to novel honeycomb hybrid design), which serves as marker facilitating precise positioning and deployment at the desired location (*Figure 2*). The lower closed cells of the valve frame are covered externally with a protective sealing cuff of

Figure 1: The MyVal™ transcatheter heart valve system



PET = polyethylene terephthalate; RO = XXX.

Figure 2: Schematic representation of crimped MyVal™ transcatheter heart valve system



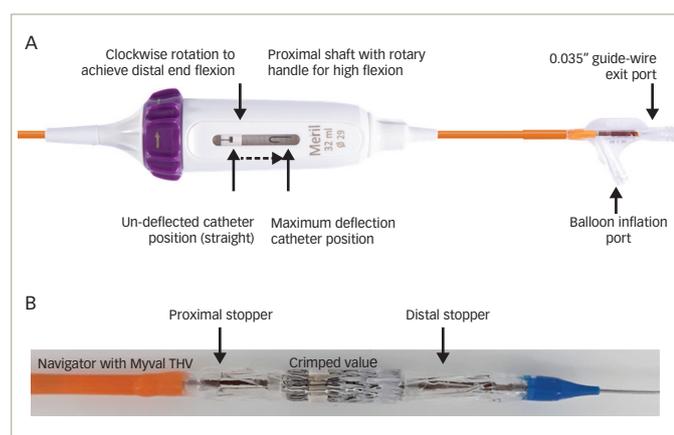
The characteristic bands may not be visible if the THV system is not co-axial to the annular plane. In this case, the THV landing zone must be referenced using the mid-balloon marker, which has to be kept at 3 mm above the annular plane. LV = left ventricle; THV = transcatheter heart valve.

polyethylene terephthalate to form an external buffering, which provides a protective sealing cuff to reduce, or nearly eliminate, paravalvular leak.

The MyVal THV is available in various sizes – standard (20, 23, 26 and 29 mm), intermediate (21.5, 24.5 and 27.5 mm) and extra-large (30.5 and 32 mm). It is worth noting that the MyVal THV size 32 mm is DCGI approved and 30.5 mm is pending DCGI approval. MyVal THV sizes 30.5 mm and

32 mm are currently not CE-marked. The availability of intermediate sizes facilitates precise sizing to match the annulus, thereby reducing oversizing risks. Also, the availability of the extreme small and large size enables the treatment of a range of aortic annulus diameters from 18.5 mm to 29.9 mm with standard and intermediate MyVal THV sizes. The treatable range further expands to 32.7 mm with the extra-large size of MyVal THV.

Figure 3: Navigator™ – the delivery system of MyVal transcatheter heart valve system



A. Proximal shaft with rotary handle for hi-flexion; B. Distal tip. THV = transcatheter heart valve.

The delivery catheter

The valve delivery system, named Navigator (Meril Life Sciences Pvt. Ltd., Gujarat, India), (Figure 3) has a unique design characterised by a proximal deep flexion handle and a distal over-the-wire balloon, on which the MyVal THV is pre-mounted externally. External crimping and mounting on the balloon simplifies the procedure for the operator. The Navigator system on either end has two counter-opposing soft stoppers that create a shallow, low-profile crimping zone to provide a precise and snug fit of the crimped valve. These stoppers prevent inadvertent migration of the valve and minimise the risk of valve dislodgement during its advancement through the sheath and the aorta. The Navigator system has a high-flexion feature which allows flexion of the distal catheter system and reduces the risk of trauma to the aortic arch during advancement, and thereby possibly reduces the risk of peri-procedural stroke. Additionally, this flexion feature facilitates crossing a difficult and angulated or horizontal annulus. Another important feature of the balloon is that it has two internal expansion ports, which facilitates simultaneous expansion, distally and proximally (like a dog-bone), which stabilises the valve during deployment and ensures precise placement.

The introducer sheath

The Python™ introducer sheath (Meril Life Sciences Pvt. Ltd., Gujarat, India) is a 14 Fr sheath which expands momentarily (like a python swallowing prey) to allow passage of the MyVal THV crimped on balloon catheter. Two separate, calibrated loading tubes ensure the temporary opening of haemostatic valves in the proximal port, allowing smooth passage of the crimped MyVal THV System. The unique feature of this sheath allows the complete retrieval of an undeployed MyVal THV in the event of a difficult crossing or inadvertent loss of the LV wire position, and facilitates insertion of it again through the sheath (Figures 4–7).

The MyVal THV is typically designed to be delivered through the transfemoral approach; however, trans-subclavian, transaortic, and trans-carotid approaches have also been used.

Pre-clinical studies

Initial animal studies were conducted as per standard protocols. Successful aortic anchoring, along with acute valve functionality of the MyVal THV (n=11) was achieved in all the ovine TAVI aortic banding models.¹³ The MyVal THV system has been successfully tested for its

Figure 4: Aortogram showing severe calcific aortic stenosis



Figure 5: Valve in position with alternating dark and light bands visible



functionality in robust and aggressive *in vitro* bench models as prescribed by ISO 5480-3 tests. Effective orifice area (EOA), pre-accelerated wear test for the valves ranged between 2.63 and 2.99 cm², post-accelerated wear test EOAs for the valves range between 1.90 and 2.14 cm². Twenty-eight days follow-up with transthoracic echocardiography showed good valve functionality. The animals were followed-up on days 30, day 90 and 180. Long-term evaluation of the MyVal THV in the pre-clinical setting showed good haemodynamic performance (mean pressure gradient 21.9 ± 11 mmHg, Vmax 3.3 ± 1 m/s, and ejection

Figure 6: Implantation of the valve

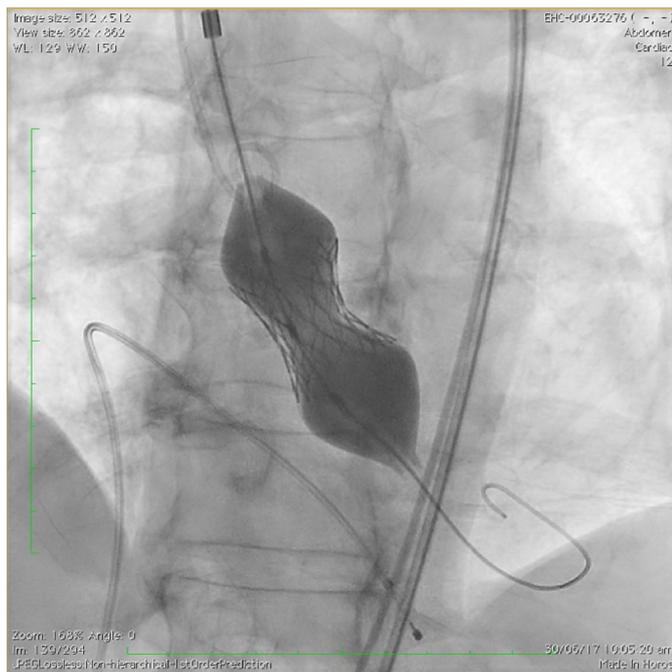


Figure 7: Valve in position, no paravalvular leak on aortogram



fraction $53.3 \pm 6\%$) at 6 months follow-up with advanced healing and no instances of excessive cusp calcification.¹⁴ There was no evidence of thrombus/embolization or structural abnormality in the valve and its components.

Clinical experience with the MyVal transcatheter heart valve system

The first in-human MyVal-1 study (Table 1) was a prospective, multicentre, single-arm, open-label study, conducted at 14 clinical sites across India.¹²

The study assessed the safety and effectiveness of the MyVal THV in 30 patients with severe aortic stenosis who were classed as intermediate or high-risk for surgery. Clinical follow-up and echocardiography were performed post-procedure and for up to 12 months after. The safety endpoint was Kaplan–Meier survival at 12 months follow-up. Efficacy endpoints included improvement in New York Heart Association (NYHA) functional classification, EOA, and 6-minute walk test from baseline and 12 months follow-up. The study also determined quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire.

The mean age of patients was 75.5 ± 6.7 years, with mean Society of Thoracic Surgeons score of $6.4 \pm 1.8\%$. It is noteworthy that 70% of patients had NYHA functional class III/IV. Post-procedural echocardiography showed significant improvement of EOA (1.7 ± 0.3 cm² versus 0.6 ± 0.2 cm², $p < 0.0001$) and mean aortic-valve gradient (8.0 ± 2.7 mmHg versus 47.4 ± 8.8 mmHg, $p < 0.0001$) as compared to pre-procedure. Haemodynamic performance of the valve sustained at 12 months, with EOA of 1.8 ± 0.3 cm², peak aortic-valve gradient of 20.3 ± 5.9 mmHg, and mean aortic-valve gradient of 12.0 ± 3.3 mmHg.

At 12 months clinical follow-up, reported all-cause mortality was four patients (13.3%). Of the four all-cause mortality cases, one patient died due to a vascular complication leading to acute renal failure post-procedure, one patient died due to septicaemia at 6 months follow-up, one patient died due to coronary artery disease with hypertension, and death related to a non-cardiac event was reported in another patient at 12 months follow-up. Major vascular complications were observed in two patients post procedure: one non-disabling stroke; no myocardial infarction, haemolysis, thrombosis, or valve migration was reported in any of the patients. None of the patients required a new permanent pacemaker at 12 months follow-up. NYHA functional class improvement was noted in all the patients at 12 months follow-up. There was also a substantial improvement in quality of life (36.6 ± 11.0 versus 65.9 ± 11.4) and the 6-minute walk test (148.0 ± 87.4 versus 336.0 ± 202.9 m) from baseline to 12 months follow-up.

The MyVal-1 study was further extended to include 100 patients from over 30 sites in India (Table 2). At 6 months follow-up, 6-minute walk test and Kansas City Cardiomyopathy Questionnaire scores were improved compared to baseline.¹⁵ There were significant improvements in the EOA, mean aortic-valve gradient, peak aortic-valve gradient and trans-aortic velocity from baseline to 6 months post-procedure. The overall 6-month all-cause mortality was 9% and stroke was 2%. The rate of new permanent pacemaker implantation was 2% (one patient had right bundle branch block pre-procedure). There was no case of myocardial infarction at 6 months follow-up.

The results of MyVal-1 study demonstrated the primary safety and efficacy of the MyVal THV at 6 months post-procedure. With more than 1,300 implants in Asia and Europe, experience from unpublished registries as well as our own experience have shown successful results with ease of deployment in a wide range of complex anatomies, including bicuspid aortic valves with low complications rates.

Future directions

With very promising initial results, the MyVal THV system now needs to be studied in a larger patient population involving long-term follow-up. To achieve this, a pivotal randomised trial, the LANDMARK TRIAL, is expected to start by December 2020, which will compare

Table 1: Clinical outcomes of the first 30 patients enrolled in the MyVal-1 study

Event Type	Follow-up (n=30)			
	Post-procedure	30-day	6-month	12-month
Major vascular complications	2 (6.7)	2 (6.7)	2 (6.7)	2 (6.7)
All-cause mortality	1 (3.3)*	1 (3.3)	2 (6.7)	4 (13.3)
Stroke (non-disabling)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New permanent pacemaker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Device associated and/or procedure-associated adverse cardiac events	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)
Early safety (at 30 days) as per VARC-2†	-	4 (13.3)	-	-
Clinical efficacy (after 30 days) as per VARC-2‡	-	-	2 (6.7)	4 (13.3)
Kidney dysfunction	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)
Repeat hospitalisation	0 (0.0)	3 (10.0)	3 (10.0)§	3 (10.0)

Values are presented as n (%).

*Patient died due to kidney dysfunction.

†Early safety (at 30 days): all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury – stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure (BAV, TAVI, SVAR).

‡Clinical efficacy (after 30 days): all-cause mortality, all stroke (disabling and non-disabling), hospitalisations for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve-related dysfunction (mean aortic-valve gradient ≥ 20 mmHg, EOA ≤ 0.9 – 1.1 cm² and/or DVI < 0.35 m/s, and/or moderate or severe prosthetic valve regurgitation).

§One patient reported gastroenteritis, one patient had access site complications and one patient reported fracture in left femur.

BAV = bicuspid aortic valve; DVI = Doppler velocity index; EOA = effective orifice area; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403-18.

Table 2: Outcomes of 100 patients enrolled in the MyVal-1 study

Event (%)	Follow-up (n=100)			
	Baseline	Post-procedure	1-month	6-month
Clinical outcomes				
Survival	-	98	97	91
All-cause mortality	-	2	3	9
Stroke	-	1	2	2
Life-threatening or disabling bleeding	-	1	1	1
Major vascular complications	-	1	1	1
Minor vascular complications	-	2	2	2
Acute renal failure	-	2	2	2
Myocardial infarction	-	0	0	0
Repeat hospitalisation	-	NA	8	10
New permanent pacemaker	-	2*	2	2
Endocarditis	-	0	0	1
Echocardiographic findings				
Mean aortic-valve gradient (mmHg)	47.4 \pm 8.8	8.0 \pm 2.7	8.8 \pm 2.5	10.5 \pm 2.6
Peak aortic-valve gradient (mmHg)	71.7 \pm 13.0	14.4 \pm 2.4	15.7 \pm 2.8	17.9 \pm 2.9
Effective orifice area (cm ²)	0.6 \pm 0.2	1.7 \pm 0.3	1.7 \pm 0.5	1.8 \pm 0.5
Mean LVEF	45.5 \pm 11.5	47.8 \pm 11.1	48.6 \pm 8.9	48.8 \pm 8.0
Trans-aortic velocity (m/s)	4.5 \pm 0.4	1.9 \pm 0.4	1.8 \pm 0.4	1.8 \pm 0.3
Moderate or severe mitral regurgitation (n)	2	0	0	0
Aortic regurgitation (n)	-	0	0	0

*One patient had right bundle branch block pre-procedure

Values are presented as n or mean \pm SD

LVEF = left ventricular ejection fraction; SD = standard deviation.

the MyVal THV to the most commonly used THV systems. The ongoing comparison of the MyVal THV with SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) is being studied in the MATCH-BALL trial (ClinicalTrials.gov Identifier: NCT04548726), under the hypothesis that there are differences in terms of transvalvular gradients and residual

paravalvular leak amongst different balloon-expandable TAVI devices available in the market. The aim of the MATCH-BALL trial is to compare the hemodynamic performance of these two balloon-expandable TAVI devices.

LANDMARK is a prospective, randomised controlled, non-inferiority trial, designed to compare the MyVal THV with newer-generation contemporary valves (SAPIEN THV series and Evolut™ THV series [Medtronic, Dublin, Ireland]). The trial is expected to enrol 768 patients with severe symptomatic native aortic valve stenosis. Patients will be randomised in a 1:1 ratio to receive either the MyVal THV or contemporary valves (SAPIEN THV series or Evolut THV series). The primary endpoint of the trial is a combined safety and effectiveness, which is a composite of all-cause mortality and stroke, life-threatening/disabling bleeding complications, major vascular complications, acute kidney injury, moderate/severe prosthetic valve regurgitation, and requirement of new permanent pacemaker implantation at 30 days follow-up. The trial was due to start in the first quarter of 2020 but has been delayed because of the COVID-19 pandemic. It is expected to start enrolment in December 2020.

Other real-world registries, which are well on the way, are MyVal European study (n=200 patients from approximately 15 sites across Europe) and MyVal Global (n=1,000 patients from 100 clinical sites across the globe).

These registries hope to shed light on the safety and efficacy of MyVal THV in contemporary clinical practice.

Conclusion

TAVR has become the standard of care for patients with symptomatic severe aortic stenosis. Continuous improvements in technology over the earlier generations of THVs have led to improved efficacy and safety, making this technology available to wider population. The MyVal THV is a newer-generation, CE-marked balloon-expandable valve, consisting of tri-leaflet bovine pericardial leaflets, supported by a nickel-cobalt alloy frame, delivered through a high-flexion Navigator balloon catheter system. Early results from the MyVal-1 first in-human trial are promising, with excellent procedural success, precise deployment and good outcomes in short-term follow-up. Longer term follow-up and ongoing randomised controlled trials and real-world registries with the MyVal THV are expected to further support the safety and efficacy, and expand its indication across the world. 

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